Communications

Reaction Mechanisms

cis-Bromination of Alkynes without Cationic Intermediates**

Rainer Herges,* Andrea Papafilippopoulos, Kirsten Hess, Cinzia Chiappe, Dieter Lenoir,* and Heiner Detert*

Dedicated to Professor Herbert Meier on the occasion of his 65th birthday

The textbook mechanism of the *trans*-bromination of alkenes and alkynes via a more or less symmetrically bridged bromonium ion does not always apply. Even in the parent system, the reaction of bromine with ethylene, this mechanism is not correct. Highly pure bromine reacts with ethylene in anhydrous dichloromethane only very slowly at room

[*]	Prof. R. Herges, Dr. A. Papafilippopoulos, K. Hess
	Institut für Organische Chemie
	Christian-Albrechts-Universität zu Kiel
	Otto-Hahn-Platz 4, 24118 Kiel (Germany)
	Fax: (+ 49) 431-880-2440
	E-mail: rherges@oc.uni-kiel.de
	Prof. D. Lenoir
	Institut für Ökologische Chemie
	GSF-Forschungszentrum für Umwelt und Gesundheit
	Postfach 1129, 85778 Neuherberg (Germany)
	Fax: (+49) 89-3187-3371
	E-mail: lenoir@gsf.de
	Dr. H. Detert
	Institut für Organische Chemie
	Johannes Gutenberg-Universität
	Duesbergweg 10–14, 55099 Mainz (Germany)
	Fax: (+49) 6131-3925396
	E-mail: detert@mail.uni-mainz.de
	Prof. C. Chiappe
	Dipartimento di Chimica Bioorganica e Biofarmacia
	Università di Pisa
	Via Bonanno 33, 56126 Pisa (Italy)
[**]	We are grateful to the Fonds der Chemischen Industrie and the
	Deutsche Forschungsgemeinschaft for financial support.
	Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

DOI: 10.1002/anie.200461632

temperature. Such mixtures are perfectly stable up to several days. As soon as light or traces of acids initiate the reaction, formation of 1,2-dibromoethane proceeds very rapidly and autocatalytically ($t_{1/2} < 2 \text{ min}$).^[1-3]

According to the generally accepted mechanism, the stereoselective *anti* addition of bromine to alkenes and alkynes proceeds via bridged bromonium ions \mathbf{A} or bromirenium ions \mathbf{A}' (Scheme 1). Aberrations from *trans* selectivity are



trans adducts cis/trans adducts cis adducts

Scheme 1. Generally assumed intermediates in the addition of bromine to alkenes and alkynes **A** (bromonium ion), **A'** (bromirenium ion), **B** (β -bromocarbenium ion), **B'** (β -bromovinyl cation), and the tribromide adducts **C** and **C'** identified in the present work by theoretical calculations.

explained by the intermediacy of the nonbridged cationic species (**B**, **B**').^[4,5] Polar solvents and cation-stabilizing substituents favor the nonstereospecific reaction by stabilization of the β -bromocarbenium ion **B** or bromovinyl cation **B**'. In extreme cases this can result in cis/trans ratios of 1:1. The syn adduct is formed after a rotation of the bromoalkyl group or by a frontside attack to the trigonal-planar cation. In alkynes only a marginal geometrical reorientaion of the counterions Br^{-} or Br_{3}^{-} is necessary to initiate a *syn* addition to give the cis-dibromo adduct. There are, however, a number of halogen additions that proceed predominantly or even selectively cis even in nonpolar solvents. In these cases a totally different mechanism must be operative. The intermediacy of free cationic intermediates without stabilization by solvation is unlikely. A number of authors interpret the predominantly observed syn addition as the collapse of a contact ion pair composed of the tribromide anion and the corresponding carbocation **B** or **B**', which is faster than the reorientation of the $\mathrm{Br_3}^-$ and a subsequent backside attack.^[6-9]

We now present experimental work showing that the addition of bromine to strained alkynes (cyclooctyne and

tetramethylthiacycloheptyne-1,1-dioxide) gives almost exclusively *syn* products, and we present theoretical evidence that the intermediate is not a contact ion pair of Br_3^- and the vinyl cation **B**'. Instead, in solvents of low polarity the Br_3^- anion forms a covalent bond with the cationic center (Scheme 1, **C**'). This tribromide adduct is formed from a π complex and rearranges directly to the product (dibromide) without passing through a cationic intermediate.

According to calculations of Bianchini, Lenoir, and Goldberg et al.^[10] the substituents at the alkyne determine whether the bromirenium ion \mathbf{A}' or the β -bromovinyl cation \mathbf{B}' will be more stable. In phenylacetylene the vinyl cation is favored because the positive charge at the benzylic position is stabilized by delocalization. Hence, the reaction proceeds in a nonstereospecific way. In *p*-nitrophenylacetylene the positive charge at the benzylic position of \mathbf{A}' is more stable, and the reaction proceeds with *anti* selectivity. Apart from the *anti*-selective and the nonstereoselective additions there are a number of *syn* additions of bromine to alkynes. Uemura et al. observed the exclusive formation of the *cis*-dibromo adduct after the reaction of *tert*-butylphenylacetylene (1) with bromine in chloroform at $-50 \,^{\circ}\text{C}$ (Scheme 2).^[11] Only after long reaction



Scheme 2. Alkynes that selectively add bromine in a syn fashion forming a *cis*-dibromoalkene.

times and higher temperatures is the thermodynamically more stable and sterically less hindered *trans*-dibromoalkene formed. Selectively *syn* additions of bromine are also observed for the reaction with alkyl propiolate **2** (which is deactivated compared to alkyl- and aryl-substituted alkynes).^[12,13] When the bromination is conducted in chloroform at 70 °C and with reaction times of 1–3 h only the *cis*dibromo adducts are formed. *trans*-Dibromopropenoates can be obtained selectively by reaction with pyridinium tribromide and bromine.

The *syn* selectivity obviously holds also for the addition of bromine to strained cycloalkynes. Krebs et al. observed the formation of only the *cis*-dibromo adducts in the bromination of dibenzocyclooctyne $\mathbf{3}$,^[14] and 3,3,6,6-tetramethylthiacycloheptyne-1,1-dioxide ($\mathbf{4}$)^[15] in chloroform or dichloromethane. According to our investigations, cyclooctyne ($\mathbf{5}$) gives 25% of the *cis*-dibromide at -40 °C in CDCl₃ (detected by independent synthesis and X-ray analysis, see the Supporting Information) and only 3% of the *trans* product. Besides that, bromocyclooctene is formed by addition of HBr (for experimental details see the Supporting Information). A single

Communications

electron transfer (SET) mechanism leading to the *cis* product is very unlikely. Kinetic measurements show that the reaction is of first order in cyclooctyne and second order in bromine. Moreover, neither the reaction rate nor the reaction order is changed upon addition of radical scavengers.^[16] The addition of tetrammonium tribromide in polar solvents yields only the *trans*-dibromide (see the Supporting Information). Wittig and Dorsch observed the formation of the *cis* product upon reaction with bromine and iron powder.^[17]

To elucidate the mechanism of the *syn* addition we performed extensive density functional theory (DFT) calculations first on the potential energy surface of the parent system acetylene+2Br₂ and also on the potential energy surface of cyclooctyne+2Br₂ at the B3LYP/6-31G*+ZPE and B3LYP/6-31G(2df)+ZPE levels of theory.^[18] The stationary points were characterized by harmonic frequency analyses, and the topology of the potential energy surface was checked by IRC calculations. To locate the stationary points, we used numerous grid calculations as well as other methods.

In agreement with experimental observations of Bianchini et al.^[10] π complexes are formed initially. As in the case of alkenes the reactive complexes have the stoichiometry

acetylene-2 Br₂.^[19] According to the calculations three different 1:2 complexes are in equilibrium; these complexes are 8.62–10.79 kcalmol⁻¹ (B3LYP/6-31G*) and 6.40–8.02 kcal mol⁻¹ (B3LYP/6-31G(2df)) more stable than the separated reactants (Scheme 3). In the L-shaped complex **6**, a bromine molecule is coordinated perpendicularly to one of the π bonds and an additional bromine molecule is bound to the first at an angle of 90° (Scheme 3, Figure 1). According to our calculations this is the starting point for the formation of the bromirenium ion and the polar mechanisms.

Starting from the most stable π complex **7** and proceeding with an activation energy $((7\rightarrow 9)^{+})$ of 23.7 kcalmol⁻¹ (B3LYP/6-31G*) or 24.7 kcalmol⁻¹ (B3LYP/6-31G(2df)), the structurally interesting tribromide adduct **10** is formed. There is a very flat minimum **9** between the transition state $(7\rightarrow 9)^{+}$ and **10**, which rearranges to **10** with an activation barrier of only 0.3 kcalmol⁻¹ (B3LYP/6-31G*) or 0.1 kcal mol⁻¹ (B3LYP/6-31G(2df)) and which therefore does not have any chemically interpretable significance.

The tribromide adduct **10** diverges from the usual valence schemes of bromine in organic compounds. The central bromine atom in the Br_3^- unit is bound to the neighboring



Scheme 3. Comparison of the bromirenium ion with intermediates in nonionic mechanisms for the bromination of acetylene. The energies of the stationary points in a vacuum (left) and the SP solvent energies in dichloromethane (B3LYP/6-31G*+ZPE in kcalmol⁻¹, right) are relative to the most stable π complex 7. The energies in vacuo and in dichloromethane at B3LYP/6-31G(2df) are given in parentheses (relative to the π complex 7 at the same level of theory).

1414 © 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

www.angewandte.org



Figure 1. Geometries (B3LYP/6-31G*) of selected stationary points on the potential energy surface of the addition of bromine to acetylene.

the reactants and is a well-defined minimum (also at the MP2/ 6-31G* level of theory).

The dibromo adduct 11 is formed from 10 by a "shift" of the Br₃⁻ unit and elimination of Br₂. The activation barrier for this reaction is 20.3 kcalmol⁻¹ (B3LYP/6-31G*) or 21.8 kcal mol^{-1} (B3LYP/6-31G(2df)). The product complex **11** is more stable than the isolated molecules (dibromoethene and bromine) by 6 kcal mol^{-1} . There is also a concerted sixcenter pericyclic transition state $(8 \rightarrow 11)^{\pm}$, which leads to the product 11; however, with an activation barrier of $\Delta H^{\dagger} =$ 26.3 kcalmol⁻¹ (B3LYP/6-31G*) or 28.0 kcalmol⁻¹ (B3LYP/ 6-31G(2df)), this reaction pathway is significantly less favorable. The "textbook intermediate", the bromirenium ion 12, is considerably more difficult to describe theoretically than the less polar species. The relative energies given in Scheme 3 and Table 1 are therefore less reliable. The relative energy $(134.6 \text{ kcal mol}^{-1} \text{ (B3LYP/6-31G*)} \text{ or } 133.4 \text{ kcal mol}^{-1}$ (B3LYP/6-31G(2df)) of the separated ion pair 12a can be considered as the upper limit. As the lower limit, one can consider the twofold hydrogen-bonded ion pair $12b^{[22]}$ with 21.2 or 22.2 kcal mol^{-1} .

Single-point energy (SP) solvent calculations using Tomasi's Polarized Continuum Model (PCM)^[23–25] reveal that the activation barrier $(7\rightarrow 9)^{+}$ leading to the tribromide adduct **10** is drastically reduced even by moderately polar media (Table 1). The same applies to the bromirenium ion **12**. The very large energy difference between **12a** and **12b** in vacuo (103.5 kcalmol⁻¹) is, as expected, drastically reduced in polar solvents (10.8 kcalmol⁻¹, B3LYP/6-31G(2df)). However, even in water the energy of **12b** is still 4.5 kcalmol⁻¹ higher than the transition state $(7\rightarrow 9)^{+}$ that leads to the tribromide adduct **10**. The latter is at least 40 kcalmol⁻¹ more stable than the bromirenium ion **12**.

carbon atom with a bond length of only 1.921 Å. (Figure 1). This bond is significantly shorter than that in the π complex (3.081 Å) and not much longer than a "normal" C–Br bond (\approx 1.89 Å). Also the charges (NBO analysis)^[20] indicate a covalent C–Br bond and do not support a contact ion pair. The two C atoms with a charge of -0.04 are almost neutral. The central Br bearing the

 Table 1: Relative energies for the transition states and the ion pairs 12a and 12b in various solvents.^[a]

Solvent	(7 → 9) [‡]	(10→11) [‡]	(8→11) [≠]	12a	126
cyclohexane	19.48 (20.19)	4.96 (5.15)	25.43 (27.07)	83.31 (75.45)	24.08 (25.86)
dichloromethane	17.93 (17.43)	4.82 (4.35)	24.22 (25.16)	46.66 (32.99)	21.22 (22.16)
methanol	16.02 (16.71)	3.35 (4.34)	22.50 (24.81)	26.93 (23.98)	18.89 (21.23)
DMSO	16.90 (16.04)	1.64 (3.60)	20.87 (24.16)	37.77 (22.70)	17.31 (20.58)
water	15.05 (15.74)	2.72 (3.57)	21.89 (24.09)	24.41 (22.03)	18.01 (20.17)
vacuum	23.72 (24.66)	9.41 (9.21)	28.43 (29.65)	134.58 (133.43)	28.52 (29.94)

[a] Energies relative to the π complex 7; PCM-SP B3LYP/6-31G* in kcal mol⁻¹. The energies at the B3LYP/6-31G(2df) level of theory are given in parentheses.

C–Br bond has a positive charge of +0.57, which is almost compensated by the two terminal Br atoms (-0.32 and -0.31). The Br–Br bonds with 2.575 and 2.583 Å are similar in length to that in the tribromide anion (2.606 Å), and the C– C bond length of 1.327 Å corresponds that in **11** (1.330 Å). Interpreted within the simple valence bond model, the tribromide anion is a linear 22-electron species with a trigonal-planar sp³d-hybridized central Br atom. The three lone pairs occupy the equatorial positions. The interaction of one of the lone pairs with a cation therefore generates a Tshaped molecule. Despite its unusual structure^[21] the tribromide adduct **10** is more than 10 kcal mol⁻¹ more stable than Considering the relatively high barriers separating the tribromide adduct **10** from the reactants and the products, it should be possible to isolate this intermediate under suitable conditions. There is indeed evidence that a tribromide intermediate analogous to **10** is formed in the reaction of bromine with **4**. During the reaction of **4** with two equivalents of bromine at -70 °C a yellow-orange precipitate formed. When the reaction mixture was allowed to warm up to 0 °C, we observed the conversion of the complex to the *cis*-dibromo adduct. In the ¹³C NMR spectrum at -40 °C there are only two signals at 129.79 and 135.19 ppm, which indicate olefinic rather than cationic carbon atoms. The NMR data indicate

Communications

that the observed intermediate is not symmetric, in agreement with an intermediate with a tribromide structure analogous to **10**; this is in contrast to the symmetric reactant and the product of the bromination reaction. Unfortunately, however, the spectroscopic data are not sufficient to assign the structure unambiguously. All attempts to determine a crystal structure were unsuccessful.^[26]

Because of the high stability of the tribromide adduct one could expect that this species is also an intermediate in bromination reactions of alkenes. Even in very polar solvents the two conformations of the tribromide adducts **15** and **16** are significantly more stable than the bridged bromonium ion, both as a separated ion pair **18a** as well as the contact ion pair **18b** (see Scheme 4). However, the activation barrier for the



Scheme 4. Nonionic mechanisms for the bromination of acetylene. The energies of the stationary points (B3LYP/6-31G*+ZPE in kcal mol⁻¹) are relative to the most stable π complex **13**. The SP solvent energies in dichloromethane (B3LYP/6-31G* in kcal mol⁻¹) are also relative to the π complex **13**.

formation of **15** from the π complex **14**, at least in the parent system acetylene, is too high to compete with the classical mechanism via the bromonium ion. In substituted systems like acenaphthylene, which adds bromine preferentially *cis*, however, an intermediate analogous to **15** is likely.^[7,8]

Received: August 13, 2004 Revised: November 3, 2004 Published online: January 21, 2005

Keywords: alkynes · bromination · density functional calculations · electrophilic addition · reaction mechanisms

- [1] H. S. Davis, J. Am. Chem. Soc. 1928, 50, 2769-2780.
- [2] D. M. Williams, J. Chem. Soc. Abstr. 1932, 2911-2915.
- [3] S. Kammermeier, R. Herges, unpublished results.
- [4] Review on alkenes: M.-F. Ruasse, Adv. Phys. Org. Chem. 1993, 28, 207.
- [5] Review on alkynes: G. Melloni, G. Modena, U. Tonellato, Acc. Chem. Res. 1981, 14, 227–233.
- [6] M.-F. Ruasse, G. L. Moro, B. Galland, R. Bianchini, C. Chiappe, G. Bellucci, J. Am. Chem. Soc. 1997, 119, 12492–12502.
- [7] V. F. Anikin, V. V. Veduta, A. Merz, Monatsh. Chem. 1999, 130, 681–690.
- [8] G. Bellucci, C. Chiappe, R. Bianchini, P. Lemmen, D. Lenoir, *Tetrahedron* 1997, 53, 785-790.
- [9] K. Zates, H. W. Leung, J. Org. Chem. 1980, 45, 1401-1406.
- [10] R. Bianchini, C. Chiappe, G. L. Moro, D. Lenoir, P. Lemmen, N. Goldberg, *Chem. Eur. J.* **1999**, *5*, 1570–1580.
- [11] S. Uemura, H. Okazaki, M. Okano, J. Chem. Soc. Perkin Trans. 1 1978, 1278–1282.
- [12] F. Bellina, A. Carpita, M. de Santis, R. Rossi, *Tetrahedron Lett.* 1994, 35, 6913–6916.
- [13] R. Rossi, F. Bellina, A. Carpita, R. Gori, *Gazz. Chim. Ital.* 1995, 125, 381–392.
- [14] J. Odenthal, Dissertation, Universität Heidelberg, 1975.
- [15] U. Höpfner, Dissertation, Universität Heidelberg, 1979.
- [16] C. Ciappe, unpublished results.
- [17] G. Wittig, H.-L. Dorsch, Liebigs Ann. Chem. 1968, 711, 46-54.
- [18] Gaussian 98 (Revision A.11.4), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **2002**.
- [19] R. Bianchini, C. Chiappe, D. Lenoir, P. Lemmen, R. Herges, J. Grunenberg, Angew. Chem. 1997, 109, 1340–1343; Angew. Chem. Int. Ed. Engl. 1997, 36, 1284–1287.
- [20] A. E. Reed, L. A. Curtis, F. Weinhold, *Chem. Rev.* 1988, 88, 899– 926.
- [21] M. L. Munzarova, R. Hoffmann, J. Am. Chem. Soc. 2001, 123, 4787–4795.
- [22] There is no minimum for a contact ion pair composed of the bromirenium cation and a tribromide anion at the levels of theory that we applied (B3LYP/6-31G*, B3LYP/6-31(2d,f), MP2/6-31G*). The stationary point of lowest order that was found for such a species is the $C_{2\nu}$ -symmetrical structure **12b** (saddle point). Structure **12b** is suitable as a model to estimate the lower level of the relative energy because the charges come very close to each other and hence minimize the dipole moment.
- [23] S. Miertus, J. Tomasi, Chem. Phys. 1982, 65, 239-245.
- [24] S. Miertus, E. Scrocco, J. Tomasi, *Chem. Phys.* **1981**, 55, 117–129.
- [25] M. Cossi, M. Persico, J. Tomasi, J. Am. Chem. Soc. 1994, 116, 5373–5378.
- [26] We are grateful to Prof. Dr. R. Boese, Universität Essen, for his attempts to determine the X-ray structure of the intermediate in the bromination of **4**.